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10/521,040	08/16/2005	Herman Jan Tijmen Coelingh Bennink	0470-050079	6630

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EXAMINER	
CHUI, MEI PING	

ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,040	COELINGH BENNINK ET AL.	
	Examiner	Art Unit	
	MEI-PING CHUI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *19 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-62* is/are pending in the application.

4a) Of the above claim(s) *56-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/2007 and 05/09/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Action

Receipt of Amendments/Remarks filed on 11/19/2007 is acknowledged. Claims 25 and 35 have been amended. Receipt of IDS filed on 11/19/2007 is acknowledged. The newly submitted IDS has been considered and placed in the file. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL.**

Status of Claims

Accordingly, claims 25-54 are presented for examination on the merits for patentability.

Withdrawn rejections/objections

(1) The previous rejection over **claim 25**, under 35 U.S.C. 112 second paragraph as being indefinite, is withdrawn in light of the amendment filed on 11/19/2007.

Double Patenting

The previous rejection for **claims 25-28** on the ground of provisional non-statutory obviousness-type double patenting over claims 20-24 in co-pending U. S. Patent Application No. 10/532,320 is maintained.

Response to Arguments

Applicants argue that double patenting rejection over co-pending U. S. Patent Application No. 10/532,320 is premature because the conflicting claims 20-24 in the co-pending application have not been allowed. Furthermore, the co-pending U. S. Patent Application No. 10/532,320 has an October 23, 2002 priority date, whereas the instant application has a July 12, 2002 priority date. A non-statutory obviousness-type double patenting rejection is not applicable to an application with an earlier filing date because a terminal disclaimer in the instant application would not disclaim any of the patent term.

Applicant's arguments filed on 11/19/2007 have been fully considered but they are not persuasive. "The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications." See MPEP 822.01. Since the double patenting rejection is not the only rejection in the instant application; therefore, the double patenting rejection is maintained.

Claim Rejections - 35 USC § 112 second paragraph

(1) The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of **claim 44**, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claiming the subject matter which applicant regards as the invention, is maintained.

Response to Arguments

Applicant argues that "a skilled artisan would know standard analytical techniques to determine the amount of a particular aromatase inhibitor needed to suppress blood serum 17β-estradiol levels to below 10 pg per ml in a subject. The standard analytical techniques do not require a great deal of experimentation to carry out a dosage-effect study to establish the minimum dosage of aromatase inhibitor that is required to reduce blood serum 17β-estradiol levels to below 10 pg/ml. For these reasons, a skilled artisan would understand the meaning of "an effective amount" (see Remarks, page 10, lines 1-9).

Applicant's arguments filed on 11/19/2007 have been fully considered but they are not persuasive. Although to carry out a dosage-effect study to establish the minimum dosage of a single aromatase inhibitor that is required to reduce blood serum 17β-estradiol levels to below 10 pg per ml may not cause an undue experimentation using the standard analytical techniques;

however, to carry out such dosage-effect study with each and every aromatase inhibitor would cause a great deal of undue experiments because each aromatase inhibitor is different in structure and biologically effect, and would expect to have different level of inhibition with respect to the estrogen receptors. Thus, "an effective amount" that is required to reduce blood serum 17β-estradiol levels to below 10 pg per ml would be varied depending on a particular aromatase inhibitor of interested. Since the term "an effective amount" is not defined by the specification, and the specification does not provide a standard for ascertaining the requisite degree of which aromatase inhibitor is used in the method; therefore, a skilled artisan would not know the metes and bounds of which aromatase inhibitor and the effective amount are infringed. Thus, it renders the claim indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

(**1**) The rejection over **claims 25-28, 30-38, 40-48 and 50-54**, under 35 U.S.C. 103(a) as being unpatentable over Elliesen J. (U.S. Patent Application Publication No. 2002/0156059) in view of Holinka et al. (Biology of Reproduction, 1980, 22, 913-926), is maintained.

Response to Arguments

Applicant argues that: (**i**) Elliesen, J. does not teach a method for treating or prophylactically treating estrogen-sensitive tumours because Elliesen, J. teaches that the use of the pharmaceutical preparation in the form of an estrogen replacement therapy "do not increase or even reduce the risk of breast cancer" (see Remarks, page 12, first paragraph); (**ii**) Elliesen, J. teaches an estrogen that is different than the estrogenic formula, as instantly claimed; (**iii**) Applicant also argues that "the mere fact that Holinka et al. concluded that estetrol (E4) and tamoxifen have estrogenic effects on immature rat uteri and is capable of stimulating uterine growth does not mean that estetrol has comparable estrogenic activity as natural" (see Remarks: page 13, first paragraph).

Applicant's arguments filed on 11/19/2007 have been fully considered but they are not persuasive. First, Elliesen, J. teaches a method of long-term treatment in the form of an estrogen

replacement therapy, wherein the "pharmaceutical preparations do not increase the risk of breast cancer since they prevent a stimulation of the mammary glands due to the increased estrogen in tissue concentrations" (page 1, [0001], line 12-15); and "the present pharmaceutical combination preparation ..... the risk of breast cancer is simultaneously reduced" (page 2, [0031], line 1 and 8-9). Therefore, Elliesen, J. does not teach away the use of a pharmaceutical combination preparation comprising an estrogen compound and an aromatase inhibitor for reducing the risk of breast cancer.

Secondly, Elliesen, J. teaches the use of estriol, which is structurally similar to the estrogenic compound as instantly claimed (see office action dated on 08/17/2007, pages 15 and 16). As the Examiner stated in the office action, estriol and estetrol both exhibit estrogenic activity; thus one of ordinary skilled in the art would have been motivated to substitute estriol with estetrol with a reasonable expectation of success because estetrol and estriol are functional equivalent estrogens and can be used interchangeably (office action dated on 08/17/2007, page 17). Applicant has not provided any unexpected results to overcome the motivation based on functional equivalency (see MPEP 2114.06(II)).

Thirdly, although Holinka et al. teach that the estrogenic potency of estetrol (E4) is lower than other natural estrogens, i.e. estradiol (E2) or estriol (E3), for example; it does not mean that estriol (E3) is ineffective as an estrogenic compound compared to estetrol (E4). The prior art can be modified or combined to rejected claims as *prima facie* obvious as long as there is a reasonable expectation of success. Applicant is required to provide evidence showing there was no reasonable expectation of success may support a conclusion of obviousness (see MPEP 716.01 and 2143.02).

(2) The rejection over **claims 29, 39 and 49**, under 35 U.S.C. 103(a) as being unpatentable over Elliesen J. (U.S. Patent Application Publication No. 2002/0156059) in view of Holinka et al. (Biology of Reproduction, 1980, 22, 913-926), and further in view of Spicer et al. (U.S. Patent No. 5,340,584), is maintained.

Response to Arguments

Applicant argues that the combination of Elliesen, J. and Holinka et al. fail to teach the claimed invention for the reason as set forth above. Applicant also argues that Spicer et al. do not teach the method, as instantly claimed, for treating or prophylactically treating estrogen-sensitive tumours. Spicer et al. also do not teach the use of estetrol in a method of treating or prophylactically treating estrogen-sensitive tumours, as instantly claimed (see Remarks: page 14, third paragraph and page 15, second paragraph).

Applicant's arguments filed on 11/19/2007 have been fully considered but they are not persuasive. The examiner directs the Applicant to Spicer et al. (column 5, line 15-29), where Spicer et al. teach a method effective for treating several benign gynecological disorders, i.e. uterine fibroids and endometriosis (lines 18 and 21). Spicer et al. also teach that the reduction in the amount of compositions administered has the effect of reducing the projected rated of incidence of breast cancer, as well as reducing the incidence of various benign gynecological disorders, i.e. ovarian cancer (lines 24-29). Furthermore, Spicer et al. also teach that the

estrogenic compound(s) used in the composition can be a natural or a synthetic estrogen, i.e. estriol or estetrol (column 7, lines 10 and 12).

In conclusion, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

It is noted that claims 25 and 35 have been amended to a method of treating or prophylactically treating estrogen-sensitive tumours ..." (see Remarks: page 10, third paragraph of rejection under 35 U.S.C. § 112 first paragraph). The term "prophylactically" is "a preventive measure" that is designed and used "to prevent a disease from occurring" (see Prophylactic definition - Medical Dictionary of Popular Medical Terms: retrieved on 03/14/2008 via www.medterms.com/script/main/art.asp?articlekey=11902). Since the term "prophylactic" is defined the same as "preventive"; therefore, claims 25-44 are still construed to be directing to a method of "treating" or "preventing" estrogen-sensitive tumours in a mammal.

NEW GROUND(S) OF CLAIM REJECTIONS

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement of the Invention

Claims 25-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 25-44 while being **enabling for treating** estrogen-sensitive tumors as claimed comprising administering a therapeutically effective amount of said estrogen compound with an aromatase inhibitor, **does not reasonably provide enablement for prophylactically treating** said estrogen-sensitive tumors in aforementioned method due to the diverse origination and causes of said tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Furthermore, claim 44, which co-administering an effective amount of aromatase inhibitor to suppress blood serum 17β-estradiol level to below 10 pg/ml, is not enabled.

An analysis of whether the scope of a particular claim(s) is actually supported by the disclosure in a patent application requires a determination of whether the disclosure, at the time of filing, contained sufficient information regarding the subject matter of the claim at issue so as to enable one skilled in the pertained art to use the claimed invention without undue

experimentation. *In re Wands*, 8 USPQ 2d 140 (Fed. Cir. 1988). Therefore, the test of enablement is not whether experimentation is necessary, but rather, if experimentation is in fact necessary, whether it is reasonably considered to be undue. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). Determining the issue of enablement with respect to a claim is a question of law based on underlying factual findings. *In re Vaeck*, 20 USPQ 2d, 1444 (Fed. Cir. 1991). More particularly, there are many factors to be considered in determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, and whether any necessary experimentation is reasonably considered to be "undue". See *In re Wands* at page 1404. MPEP § 2164.01(a). The court in *In re Wands* set forth the following factors to be considered, which included, without limitation, the: 1). scope or breadth of the claims; 2). nature of the invention; 3). relative level of skill possessed by one of ordinary skill in the art; 4). state of, or the amount of knowledge in, the prior art; 5). level or degree of predictability, or a lack thereof, in the art; 6). amount of guidance or direction provided by the inventor; 7). presence or absence of working examples; and 8). quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

Scope or breadth of the claims:

The claims are broader in scope than the enabling disclosure. The specification merely discloses, without more, the method of prophylactically treating estrogen-sensitive tumors by

administering an effective amount of said estrogenic compound with an aromatase inhibitor to a mammal. However, Applicant is purporting that said estrogenic compound co-administered with an aromatase inhibitor in said method can effectively treat estrogen-sensitive tumors in a mammal, or can effectively and prophylactically treat said estrogen-sensitive tumors from occurrence, even though the multitude of these diseases are diversely originated, implicate that all causes and factors that may give rise to said tumors can be treated or prophylactically treated by administering the combination of said estrogenic compound and an aromatase inhibitor.

Nature of the invention:

The nature of the invention is directed to a method of treating or prophylactically treating estrogen-sensitive tumors in a mammal, such as breast cancer, uterine cancer, endometriosis and so on as claimed, by administering an effective amount of said estrogenic compound and an aromatase inhibitor to a mammal. For claim 44, it is directed to a method for co-administration of an effective amount of aromatase inhibitor to suppress blood serum 17β-estradiol level to below 10 pg/ml.

State of, or the amount of knowledge in, the prior art:

It is known in the current state of the art that tumors arise from many different aspects and causes, such as diet, environment or genetics, for examples. Some of these factors are being assessed as risk factors that may increase the chance of developing cancer and some of these factors are being assessed as protective factors that may decrease the chance of developing

cancer. Currently, the approach to prophylactically treating cancer is based on the assessment of risk factors and protective factors a person may encounter. However, some risk factors for cancer can be avoided, but some cannot. Likewise, increase the protective factors may only lower the risk of developing a cancer, but does not completely inhibit the occurrence of a cancer (see National Cancer Institute: Breast cancer prevention retrieved online 08/07/2007 from the internet http://www.cancer.gov/templates/doc.aspx?viewed=D972A74B-D25A-4F86-B8ED-33EB3C0450E4&version, page 1). For examples, as of to date, the cause for ovarian cancer is still unknown (see Medline Plus®: Medical Encyclopedia: Ovarian cancer retrieved online on 08/09/2007 from the internet https://www.nlm.nih.gov/medlineplus/ovariancancer.html, page 1 dated on 07/31/2007) or there is still no cure for endometriosis (see National Institute of Child Health and Human development, NIH Publication No. 02-2413 retrieved online on 08/09/2007). Since prophylactically treating a disease from occurring, one must first know the cause that induces the occurring of such disease. However, currently there is still no known method that can prophylactically treating the occurrence of some diseases, such as estrogen-sensitive tumors, for example.

With respect to claim 44, the state of the art does not teach how much aromatase inhibitor is effective in relation to the treatment.

Amount of guidance or direction provided by the inventor:

Although the instant specification discloses that the administration of estetrol and tamoxifen (see specification, examples 2-5) for treating mammary tumor; it remains silent on the

use of said estrogenic compound with an aromatase inhibitor, as claimed, for the prophylactically treating said estrogenic-sensitive tumors.

For claim 44, the Examiner noticed that the instant specification discloses a pharmaceutical composition containing 0.05 mg of aromatase inhibitor anastrozole (see specification page 16, line 27-29 and page 17, line 1-3).

Presence or absence of working examples:

The specification provides some scientific data and working embodiments with respect to the administration of estetrol and tamoxifen for treating mammary tumors only (see specification, page 20-27: examples 2-5). However, in the specification, there is no working example or guidance provided for prophylactically treating the occurrence of claimed estrogen-sensitive tumors. In the same way, the specification does not provide any guidance or working embodiment with respect to the effective amount of aromatase inhibitor in order to suppress blood serum 17β-estradiol level to below 10 pg/ml, as claimed in claim 44.

Level or degree of predictability, or a lack thereof, in the art:

A high degree of unpredictability exists in the state of the art regarding how to prophylactically treating tumors formation. Risk factors evaluation, although, may help to avoid the chances of tumor formation; however, at this stage of the art, many of them are still an unsolved puzzle to the scientific field or there is lack of knowledge in the art to prophylactically

treating the occurrence of tumors due to some uncontrollable genetic risk factors. For example, women who have inherited genetic defect(s) or mutation in the *BRCA1* and *BRCA2* genes may have a higher risk of developing a breast cancer (see Breast Cancer Prevention retrieved online 08/07/2007 from the internet http://www.cancer.gov/cancertopics/pdq/prevention/breast/Patient/page 3) than those who does not inherit such genetic defect(s).

Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure:

One of ordinary skill in the art would be required to conduct an undue amount of experimentation to reasonably and accurately determine whether said estrogenic compound when co-administering with an aromatase inhibitor in corresponding instant method does in fact effectively and prophylactically treating the occurrence of said estrogenic-sensitive tumors.

For claim 44, the specification does not teach how the particular amount (0.05 mg) of aromatase inhibitor correlates to the suppression of blood serum 17β-estradiol level to below 10 pg/ml. Therefore, one of ordinary skill in the art would be required to conduct an undue amount of experimentation to predict whether the amount of 0.05 mg or other amount of anastrozole is capable of suppressing blood serum 17β-estradiol level to below 10 pg/ml.

Therefore, in conclusion, it is readily apparent from the aforementioned disclosure, in conjunction with a corresponding lack of scientific data and working embodiments regarding the prophylactically treating estrogen-sensitive tumors, is not enabled because the specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Conclusion

No claims are allowed. Applicant's amendment filed and adding new claims necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication from the Examiner should direct to Helen Mei-Ping Chui whose telephone number is 571-272-9078. The examiner can normally be reached on Monday-Thursday (7:30 am – 5:00 pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where the application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either PRIVATE PAIR or PUBLIC PAIR. Status information for unpublished applications is available through PRIVATE PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the PRIVATE PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sharmila Gollamudi Landau/

Primary Examiner, Art Unit 1611